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The discovery of *N*-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZD6703), a clinical p38α MAP kinase inhibitor for the treatment of inflammatory diseases

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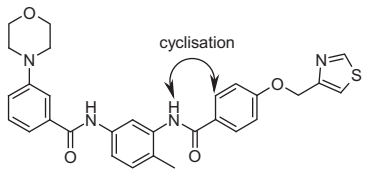
ABSTRACT

A novel, potent and selective quinazolinone series of inhibitors of p38α MAP kinase has been identified. Modifications designed to address the issues of poor aqueous solubility and high plasma protein binding as well as embedded aniline functionalities resulted in the identification of a clinical candidate *N*-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZD6703). Optimisation was guided by understanding of the binding modes from X-ray crystallographic studies which showed a switch from DFG 'out' to DFG 'in' as the inhibitor size was reduced to improve overall properties.

p38α mitogen-activated protein kinase (MAPK) plays a critical role in the regulation of pro-inflammatory cytokines including tumour necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β), the excessive production of which has been linked to a variety of inflammatory processes in a broad range of diseases including rheumatoid arthritis, psoriasis, inflammatory bowel disease, multiple sclerosis, ischaemia, Alzheimer's disease, and neuropathic pain.[1] The early reports of the biology of p38α together with the pyridylimidazole-based inhibitors[2] precipitated an enormous effort from many laboratories to discover and develop drugs utilising this mechanism.[3] The effectiveness of biological cytokine blocking agents such as etanercept, infliximab, and anakinra in treating rheumatoid arthritis and other autoimmune diseases[4] offered the hope that targeting of these cytokines through inhibition of p38α would provide an oral, small molecule alternative. Disappointingly however, although a number of compounds from diverse chemical series have progressed into clinical trials none has yet demonstrated that inhibition of p38α can deliver a safe and efficacious treatment of inflammatory diseases.[5]

A previous disclosure from this laboratory described the discovery of a novel series of bisamide inhibitors of p38, exemplified by compound **1**.[6] Compound **1** showed potent inhibition of p38 kinase and low micromolar inhibition of LPS-stimulated TNF-α in human whole blood (Table 1) as well as cytokine inhibitory activity in vivo.[6] However aqueous solubility was poor (0.54 μM, thermodynamic solubility measured in 0.1 M phosphate pH 7.4 buffer at 25 °C for 24 h) and plasma protein binding was rather high (2% free). In addition we were concerned about the possibility of enzymatic cleavage of one or other of the amide bonds in vivo with concomitant release of a potentially mutagenic aniline species[7] or for aniline impurities to be carried through the manufacture of the advanced pharmaceutical intermediate.[8]



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We hypothesised that cyclisation from an amide nitrogen to the adjacent carbonyl-bearing phenyl ring would retain the planar conformation of the benzamide while removing one potential aniline cleavage product. Previous investigations in the bisamide series had also suggested that the terminal heteroarylmethoxy group could be removed without significant loss in potency and replaced with basic amine-containing side chains/rings which improved solubility and plasma protein binding. A 6-*N*-methyl piperazinyl group was selected because it is a weakly basic group which should

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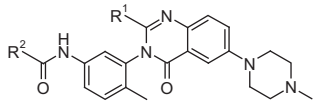
Table 1
Inhibition of p38 kinase and LPS induced TNF-α release in human whole blood (HWB) and human hepatocyte intrinsic clearance for selected compounds

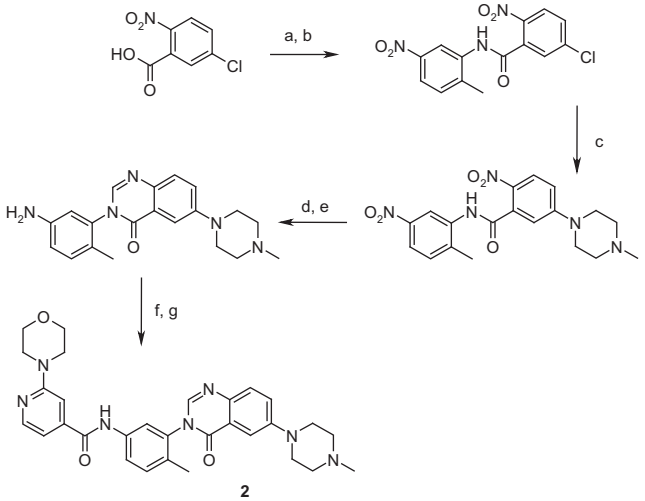


Compound	R^1	R^2	p38α IC_{50}[a] (nM)	HWB IC_{50}[a] (μM)	HH CL_{int} (μL/min/10^6 cells)
1	—	—	18	1.5	—
2	H	2-Morpholino-4-pyridyl	35	0.42	17
3	Me	2-Morpholino-4-pyridyl	220	3	—
4	H	3-Morpholinophenyl	89	0.90	20
5	H	Phenyl	15	0.64	6
6	Me	Phenyl	1941	>50	—
7	H	2-Methoxyphenyl	108	1.8	5
8	H	3-Methoxyphenyl	65	3.4	—
9	H	3-Cyanophenyl	20	1.4	<3
10	H	4-Cyanophenyl	9.0	0.18	<3
11	Me	4-Cyanophenyl	708	9.1	—
12	H	2-Fluorophenyl	14	0.50	7
13	H	3-Fluorophenyl	29	1.2	11
14	H	4-Tetrahydropyranyl	484	4.2	—
15	H	Cyclobutyl	155	2.9	—
16	H	Cyclopropyl	108	1.0	5
17	H	3-Pyridyl	525	9.0	—
18	H	5-Isoxazolyl	25	0.11	5
19	H	4-Thiazolyl	181	1.3	7
20	H	5-Thiazolyl	26	0.73	<3
21	H	2-Thiazolyl	>2200	>50	—
22	H	3-Furanyl	9.0	0.11	5
23	Me	3-Furanyl	1535	12	—

[a] IC_{50}'s were derived from triplicate measurements whose standard errors were normally <5% in a given assay.

improve physical properties and because it could be readily introduced in the course of the synthesis.

Quinazolinones **2**–**23** (Table 1) were prepared as exemplified by the synthesis of **2** in Scheme 1. The *N*-methyl piperazinyl group was introduced by S_NAr reaction using the para nitro as an activating group (step c). Subsequent reduction of the nitro by palladium



Scheme 1. Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt; (b) 2-methyl-5-nitroaniline, NEt_3, CH_2Cl_2, rt (99% over two steps); (c) *N*-methyl piperazine, 100 °C (83%); (d) H_2, 10% Pd/C, MeOH, rt (80%); (e) $(OEt)_3CH$, AcOH, EtOH, 70 °C (98%); (f) 2-chloropyridine-4-carbonyl chloride, NEt_3, CH_2Cl_2, rt (91%); (g) morpholine, 100 °C (57%).

catalysed hydrogenation also reduced the nitro group which had served as a masked aniline on the other phenyl ring. Formation of the quinazolinone was achieved by cyclisation with triethylorthoformate catalysed by acetic acid. Acylation with the substituted pyridine acid chloride followed by a second S_NAr reaction to install the morpholino group completed the synthesis of **2**. The 2-methyl quinazolinone analogues **3**, **6**, **11** and **23** were prepared following the same sequence but substituting triethylorthoacetate for triethylorthoformate.

Compounds were tested in vitro for inhibition of human p38α enzyme activity and for inhibition of TNF-α in LPS-stimulated human whole blood.[9] Initial compounds in the quinazolinone series (**2**–**4**) showed moderate to good potency in the p38 and whole blood assays, similar to that seen for bisamide **1** (Table 1). Aqueous solubility was excellent for these compounds (300–900 μM). Substitution with methyl in the 2- position of the quinazolinone led to a decrease in activity (**2** vs **3**). Removal of the methyl on the central phenyl ring removed all p38 activity, as was seen for the bisamide series[6] (data not shown). These compounds had reasonable pharmacokinetic (PK) properties but rather high in vitro clearance in human hepatocytes (Table 1). We next sought to improve PK properties by reducing the molecular weight to below 500 by (i) changing the substitution on the benzamide group and (ii) replacing the phenyl with alternative groups. The morpholino group was found not to be required since the unsubstituted phenyl and its analogues bearing methoxy, cyano and fluoro substituents at various positions were active (**5**, **7–10**, **12–13**). Replacement of the phenyl ring with saturated heterocyclyl or cycloalkyl groups reduced activity (**14–16**) as did 6-membered heteroaryl groups (**17**). The SAR for 5-membered heteroaryl groups was interesting since varying both the nature and the position of the heteroatoms influenced activity significantly (**18**, thiazolyl isomers **19–21**, **22**). As before, the 2-methylquinazolinones were much less potent than their unsubstituted analogues (**6**, **11**, **23**).

Representative compounds **5**, **10** and **22** were tested in a panel of 14 other protein kinases. IC_{50}s were in all cases >50 μM showing the excellent selectivity of this class of compounds for p38.

Quinazolinones **2** and **22** were co-crystallised with inactivated p38α and the X-ray structures solved (R = 21.3% for 1.8 Å Daresbury synchrotron data and R = 21.1% for 2.3 Å in-house data, respectively).[10] The main features of this binding mode (Fig. 1) are the hydrogen bond between the amide carbonyl and the backbone amide NH of Asp168, the hydrogen bond between the amide NH and the carboxylate sidechain of Glu71, the good fit between the methyl-substituted benzene ring and the hydrophobic region (the so-called 'selectivity pocket') formed by residues Lys53 and Thr106, and the movement of the conserved kinase DFG motif (residues 166–170 in p38α) to the so-called 'DFG-out' conformation[11] to accommodate the morpholino-benzamide group. Compound **2** was the first DFG-out kinase structure determined at AstraZeneca (around the time of the first literature report of this conformation for Gleevec bound to abl kinase[11c]). As such, it spawned significant internal interest in the inhibition of protein kinases by prevention of activation.[11b] The binding mode of **2** is consistent with that reported for the related anilinoquinazoline series[12] and with bisamides such as **1**. Hence, compounds **1** and **2** are members of the type II inhibitor class.[13] The quinazolinone N1 atom is 3.8 Å from the backbone amide NH of Met109, compromising the commonly-observed hydrogen bond seen here to the hinge region. The above-mentioned polar interactions to Glu71 and Asp 168 appear to be dominant, effectively pulling the ligand away from the hinge. There is a network of hydrogen bonds between the quinazolinone carbonyl, a water molecule, the side chain nitrogen of Lys53, the amide NH of Ala34 and the amide carbonyl of Asp168.

The binding mode of compound **22** (Fig. 1) shared most of these features but with one significant difference—the reduced size of

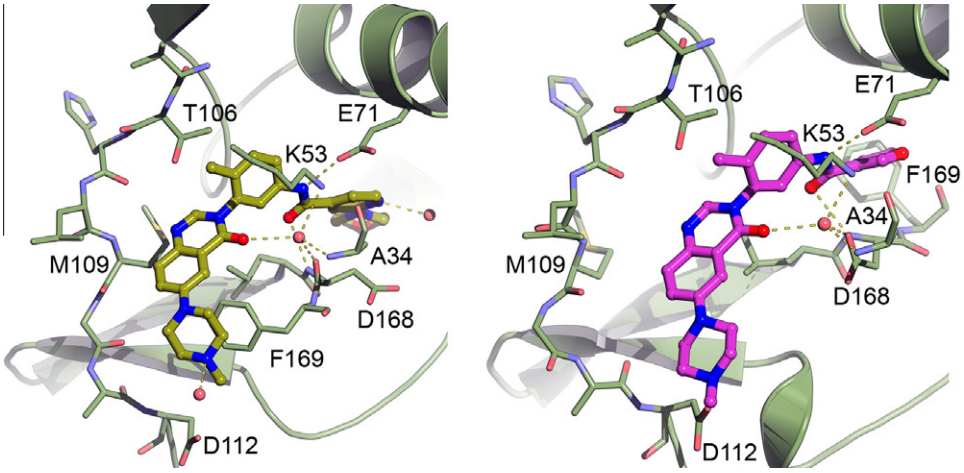
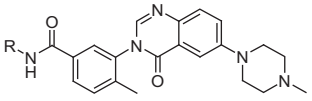


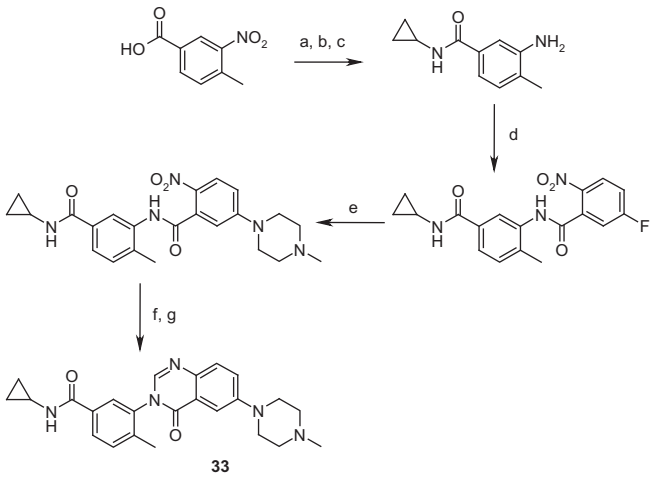
Figure 1. Co-crystal structures of p38α with compound **2** (green, PDB entry 4AA0) and compound **22** (pink, PDB entry 4AA4). Hydrogen bonds are indicated with dashed lines. See supplementary data for crystal parameters, data collection and refinement statistics.

Table 2
Inhibition of p38 kinase and LPS induced TNF-α release in human whole blood (HWB) for selected compounds



Compound	R	p38α IC_{50}[a] (nM)	HWB IC_{50}[a] (μM)
24	Phenyl	347	5.4
25	2-Thiazolyl	72	0.35
26	4-Methyl-2-thiazolyl	276	12
27	5-Methyl-2-thiazolyl	>2200	>50
28	2-(1,3,4-thiadiazolyl)	200	2
29	3-Isoxazolyl	6.7	0.011
30	5-Isoxazolyl	11	0.041
31	Cyclopentyl	692	11
32	Cyclobutyl	54	0.44
33	Cyclopropyl	16	0.027
34	Isopropyl	156	1.4
35	Ethyl	83	0.16
36	Methyl	437	1.3
37	Cyclopropylmethyl	261	2.3

[a] IC_{50}'s were derived from triplicate measurements whose standard errors were normally <5% in a given assay.



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt; (b) cyclopropylamine, NEt_3, CH_2Cl_2, rt (95% over two steps); (c) H_2, 10% Pd/C, EtOH, rt (94%); (d) 5-fluoro-2-nitrobenzoic acid, HATU, pyridine, DMF, rt (94%); (e) *N*-methyl piperazine, DMSO, 80 °C (99%); (f) H_2, 10% Pd/C, EtOH, rt (94%); (g) $(OEt)_3CH$, AcOH, EtOH, 80 °C (79% over two steps).

the amide group means it no longer induces the DFG loop movement and **22** shows the 'DFG in' conformation, making it a type I½ inhibitor.[13] The water molecule is now hydrogen bonded to the carboxylate of Asp168 rather than the backbone carbonyl. The quinazolinone N1 atom remains distant from the backbone amide NH of Met109 (5.4 Å).

In order to address the one remaining embedded aniline, the effect of reversing the amide group and replacing the N-substituent with heteroaromatic and aliphatic groups was investigated. 'Reverse amide' quinazolinones (Table 2)[14] were prepared as exemplified by the synthesis of **33** in Scheme 2.

Reversing the amide bond resulted in compounds which were active against p38 but the SAR was found to differ markedly from that observed in the previous quinazolinone series. For example, with the phenyl substituent (**24**) reversing the amide led to a drop in potency, while the 2-thiazolyl (**25**), 5-isoxazolyl (**30**), cyclobutyl (**32**) and cyclopropyl (**33**) substituents all gave an increase in potency. Substituting the thiazole ring with methyl resulted in either a small (**26**) or large (**27**) drop in potency depending on the position of substitution. The SAR for small alkyl substituents was particularly striking—going from methyl (**36**) to ethyl (**35**) increased potency, while the isopropyl (**34**) had intermediate potency and the cyclopropyl (**33**) was the most potent.[15] In their report on a related series Liu et al.[15a] rationalise the increased potency of cyclopropyl over the ethyl in terms of an increase in the NH hydrogen bond donor strength.

Reverse-amide quinazolinones **29** and **33** were co-crystallised[10] with inactivated p38α and the X-ray structures determined (R = 23.4% for 2.5 Å ESRF synchrotron data and R = 21.6% for 2.4 Å in-house data, respectively). The binding modes (Fig. 2) were very similar to that seen for type I½ compound **22**, the main differences being the presence of an additional bound water molecule hydrogen bonded to both the quinazolinone N1 and the Met109 backbone NH in **29**, and an interaction between the piperazine basic nitrogen and the amide carbonyl of Val30 in **33**.

An analysis of the in vitro data revealed a very good correlation between the enzyme potency and the potency against LPS-induced TNF-α in human whole blood corrected for plasma protein binding (Fig. 3) showing that the improvement from micromolar whole blood potency seen in bisamide **1** to nanomolar potency seen with compounds **29** and **33** can be attributed to a reduction in protein binding. On average there is a drop in activity (~fivefold) going

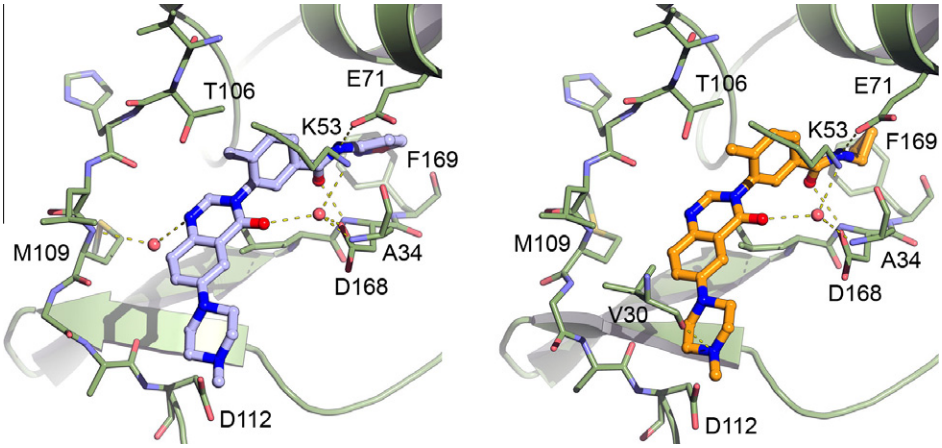


Figure 2. Co-crystal structures of p38α with compound **29** (blue, PDB entry 4AAC) and compound **33** (orange, PDB entry 4AA5). Hydrogen bonds are indicated with dashed lines. See supplementary data for crystal parameters, data collection and refinement statistics.

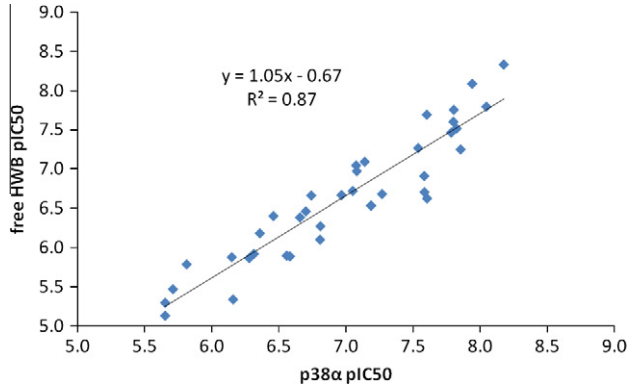


Figure 3. Plot of free human whole blood pIC_{50} versus p38α pIC_{50} with line of best fit. See supplementary data for data.

from the enzyme IC_{50} to the calculated free whole blood IC_{50}, as expected when going from inhibition of the activity in an isolated enzyme assay to inhibition of the p38 pathway in cells.

The compounds with the best in vitro properties were profiled in pharmacokinetic, pharmacodynamic and disease model experiments. Oral absorption was good in rat and dog (Table 3) and the predicted human PK was consistent with once or twice daily dosing. The compounds were orally active in vivo in an acute LPS challenge PD model in rats measuring inhibition of transient circulating TNF-α levels, (ED_{50} **2**: 5.6 mg/kg; **29**: 0.13 mg/kg; **33**: 2.1 mg/kg). Compounds **10** and **33** were active in the Lewis rat streptococcal cell wall arthritis model with ED_{50} less than 10 mg/kg once a day.[9]

Compound **33** progressed through pre-clinical safety testing and became the Phase I clinical compound AZD6703. Additional data for **33** is shown in Table 4.

In summary, a novel, potent, selective and orally available series of p38α MAP kinase inhibitors has been discovered through sequential conversion of the two embedded aniline functionalities in the bisamide series to a quinazolinone and an *N*-cyclopropyl reverse amide, respectively. Introduction of a weakly basic aryl piperazine group and reduction of molecular weight improved physical and PK properties and led to improved activity in human whole blood by reducing plasma protein binding. Structural studies revealed a switch from 'DFG-out' to 'DFG-in' modes (hence from type II to type I½ inhibitors). Taken together these results demonstrate that for this class of p38α MAP kinase inhibitors, excellent potency and selectivity is achievable with type I½ inhibitors while the additional structural features required for type II inhibitors are not readily compatible with good physical and oral PK properties. These investigations culminated in the selection of **33** as AZD6703 for Phase I clinical studies.

Table 3
Pharmacokinetic data for selected compounds

Compound	Species	Cl (mL/min/kg)	Vd_{ss} (L/kg)	$t_{½}$ (h)	F%
10	Rat	25	4.8	2.9	29
10	Dog	36	7.8	3.6	53
29	Rat	17	2.5	1.7	41
29	Dog	19	3.7	4.0	20
33	Rat	26	1.9	0.7	49
33	Dog	24	3.3	1.7	68

Table 4
Additional data for compound **33** (AZD6703)

Human hepatocyte CL_{int}	2 μL/min/10^6 cells
Human plasma protein binding	35.7% bound
MWt	417
log$D_{7.4}$	1.6
pK_a	7.6
Aqueous solubility pH7.4	20 g/mL
Caco2 A–B/B–A P_{app} at 10 μM	6/11 cm/sec × 10^{-6}
CYP450 inhibition IC_{50}	>50 μM versus 5 isoforms
hERG Inhibition IC_{50}	>100 μM
Kinase panel selectivity	>100-fold versus 35 kinases

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.04.116. These data include MOL files and InChiKeys of the most important compounds described in this article.

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